

# Influenza: Old Questions, New Answers

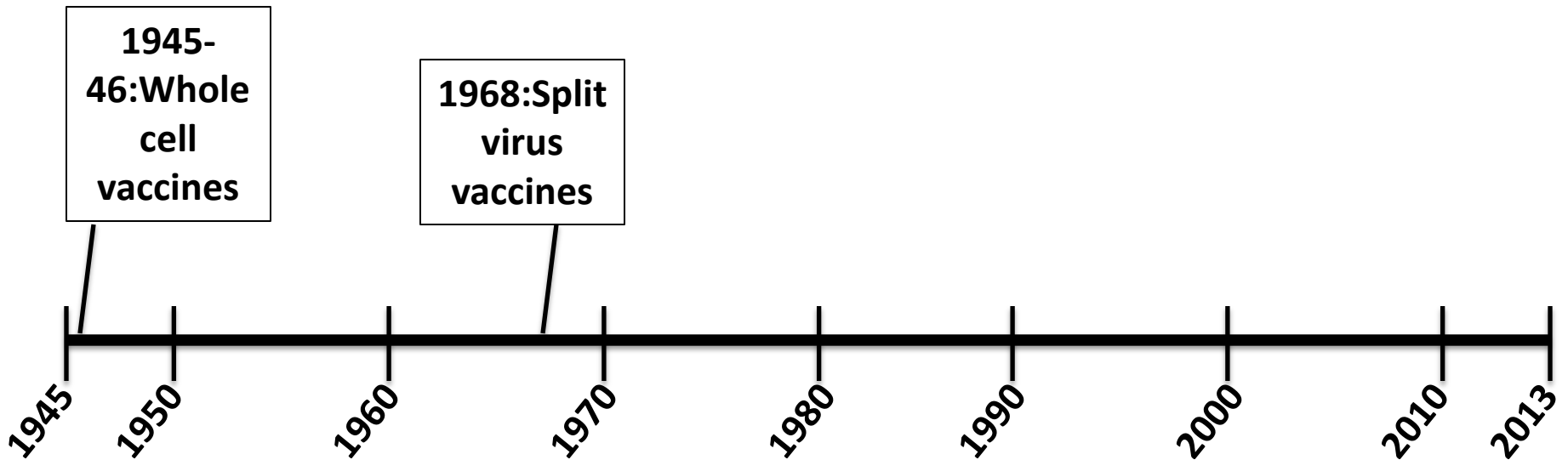


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# Interests, Conflicts, Disclosures

- Interests: many
- Conflicts: few
- Disclosures:
  - GSK: independent drug safety monitoring board

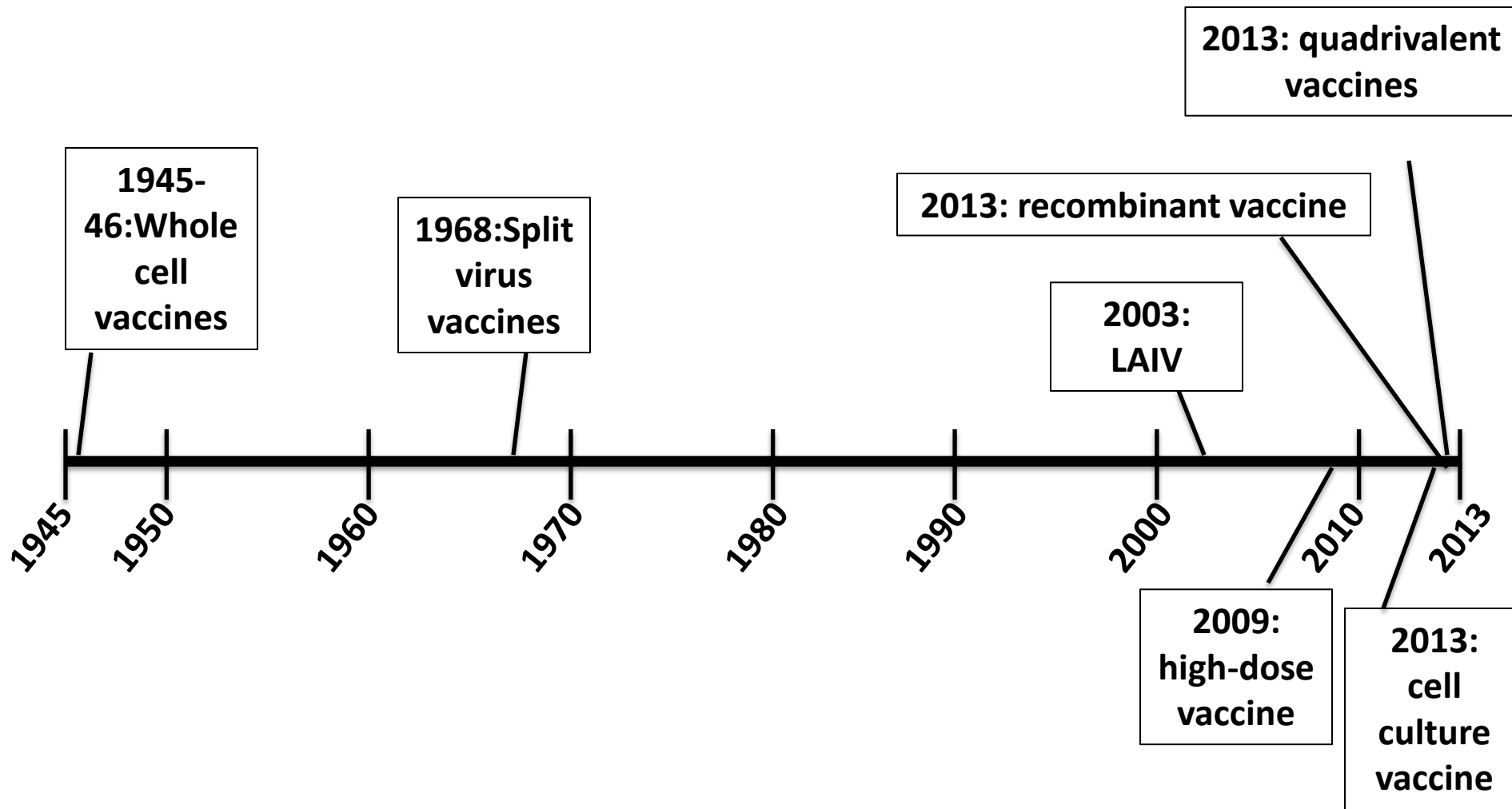
# Influenza Vaccine Development, 1945-2013



# 1968



# Influenza Vaccine Development, 1945-2013



# Influenza: Old Questions

- Which vaccine should be used?
- Who should be vaccinated?
- Do the vaccines work?
- Are the vaccines safe?
- Do the vaccines cause “the flu”?
- Aren’t there better alternatives to vaccines?
- What’s next?
- How are we doing?
- What is the greatest threat?

# 2013-14 Influenza Vaccines

Trade name	Manufacturer	Presentation	Mercury content (µg Hg/0.5 mL)	Ovalbulmin content (µg/0.5mL)	Age indications	Route
Inactivated Influenza Vaccine, Trivalent (IIV3), Standard Dose						
Afluria	CSL Limited	0.5 mL single-dose prefilled syringe	0	≤1.0	≥9 yrs <sup>†††</sup>	IM <sup>†</sup>
		5.0 mL multi-dose vial	24.5	≤1.0		
Fluarix	GlaxoSmithKline	0.5 mL single-dose prefilled syringe	0	≤0.05	≥3 yrs	IM <sup>†</sup>
Flucelvax	Novartis Vaccines and Diagnostics	0.5 mL single-dose prefilled syringe	0	NI <sup>§§§</sup>	≥18 yrs	IM <sup>†</sup>
FluLaval	ID Biomedical Corporation of Quebec (distributed by GlaxoSmithKline)	5.0 mL multi-dose vial	<25.0	≤0.3	≥3 yrs	IM <sup>†</sup>
Fluvirin	Novartis Vaccines and Diagnostics	0.5 mL single-dose prefilled syringe	≤1.0	≤1.0	≥4 yrs	IM <sup>†</sup>
		5.0 mL multi-dose vial	25.0	≤1.0		
Fluzone	Sanofi Pasteur	0.25 mL single-dose prefilled syringe	0	— <sup>¶¶¶</sup>	6–35 mos	IM <sup>†</sup>
		0.5 mL single-dose prefilled syringe	0	—	≥36 mos	IM <sup>†</sup>
		0.5 mL single-dose vial	0	—	≥36 mos	IM <sup>†</sup>
		5.0 mL multi-dose vial	25.0	—	≥6 mos	IM <sup>†</sup>
Fluzone Intradermal <sup>††</sup>	Sanofi Pasteur	0.1 mL prefilled microinjection system	0	—	18–64 yrs	ID <sup>§</sup>
Inactivated Influenza Vaccine, Trivalent (IIV3), High Dose						
Fluzone High-Dose <sup>**</sup>	Sanofi Pasteur	0.5 mL single-dose prefilled syringe	0	—	≥65 yrs	IM <sup>†</sup>
Inactivated Influenza Vaccine, Quadrivalent (IIV4), Standard Dose						
Fluarix Quadrivalent	GlaxoSmithKline	0.5 mL single-dose prefilled syringe	0	≤0.05	≥3 yrs	IM <sup>†</sup>
Flulaval Quadrivalent	ID Biomedical Corporation of Quebec (distributed by GlaxoSmithKline)	5.0 mL multi-dose vial	<25.0	≤0.3	≥3 yrs	IM <sup>†</sup>
Fluzone Quadrivalent	Sanofi Pasteur	0.25 mL single-dose prefilled syringe	0	—	6–35 mos	IM <sup>†</sup>
		0.5 mL single-dose prefilled syringe	0	—	≥36 mos	IM <sup>†</sup>
		0.5 mL single-dose vial	0	—	≥36 mos	IM <sup>†</sup>
Recombinant Influenza Vaccine, Trivalent (RIV3)						
FluBlok	Protein Sciences	0.5 mL single-dose vial	0	0	18–49 yrs	IM <sup>†</sup>
Live Attenuated Influenza Vaccine, Quadrivalent (LAIV4)						
FluMist Quadrivalent <sup>§§</sup>	MedImmune	0.2 mL single-dose prefilled intranasal sprayer	0 (per 0.2 mL)	<0.24 (per 0.2mL)	2–49 yrs <sup>***</sup>	INL

- 7 manufacturers, 13 presentations, different modes of administration, various amounts of ovalbumin, with or without mercury, blah, blah, blah...

# A “Simplified” Approach and Some New Nomenclature

- Inactivated vaccines (IIV3 or IIV4), trivalent or quadrivalent:
  - Regular dose for IM injection 15µg each antigen/0.5cc
  - High-dose (Fluzone High Dose®, Sanofi Pasteur): 60µg each antigen/0.5cc IM dose; licensed for persons aged ≥65 years
  - For intradermal administration (Fluzone Intradermal®, Sanofi Pasteur): 9µg each antigen/0.1cc ID dose; licensed for persons aged 18-64 years
- Quadrivalent live-attenuated influenza vaccine (LAIV4): FluMist®, MedImmune); licensed for persons 2-49 years
- Cell culture-based trivalent inactivated influenza vaccine (cIIV3) (Flucelvax®, Novartis); licensed for ages ≥18 years
- Recombinant trivalent hemagglutinin influenza vaccine (RIV3) (FluBlok®, Protein Sciences); licensed for aged 18-49 years

# Which Vaccine? ACIP Recommendations

- IIV vs. LAIV:
  - “No preference is indicated for LAIV versus (IIV) in [persons aged 2 through 49 years]”
  - Two exceptions:
    - “persons who care for severely immunosuppressed persons who require a protective environment should not receive LAIV given the **theoretical risk** for transmission”
    - One other...
- Regular IIV vs. high-dose IIV vs. intradermal IIV:
  - “Within specific age indications, ACIP expresses no preference for any given TIV formulation”






- August 2013, press release from Sanofi-Pasteur:  
“In a clinical trial involving about 30,000 participants, Sanofi's Fluzone High-Dose vaccine was 24.2 percent more effective in preventing influenza in older adults than a standard dose of Fluzone. Sanofi plans to submit its results for review by early 2014 and will seek to modify the label for Fluzone High-Dose vaccine to reflect the superior efficacy data.”

# Trivalent vs. Quadrivalent

- Influenza B: less antigenic diversity than influenza A
- Prior to 1980: B/Yamagata was major circulating lineage
- 1980: B/Victoria emerged
- Both lineages with drift variants circulate globally, generally with one predominating during any given season
- More difficult to predict than influenza A: mismatch between vaccine and circulating strains 6 of 12 seasons, 2001-2012
- 2012: WHO recommends quadrivalent vaccines containing both B lineages
- ACIP: “No preference is expressed for IIV4 over IIV3”.  
“Vaccination should not be delayed if only IIV3 is available.”

# Flu Vaccines Available for 2013-2014

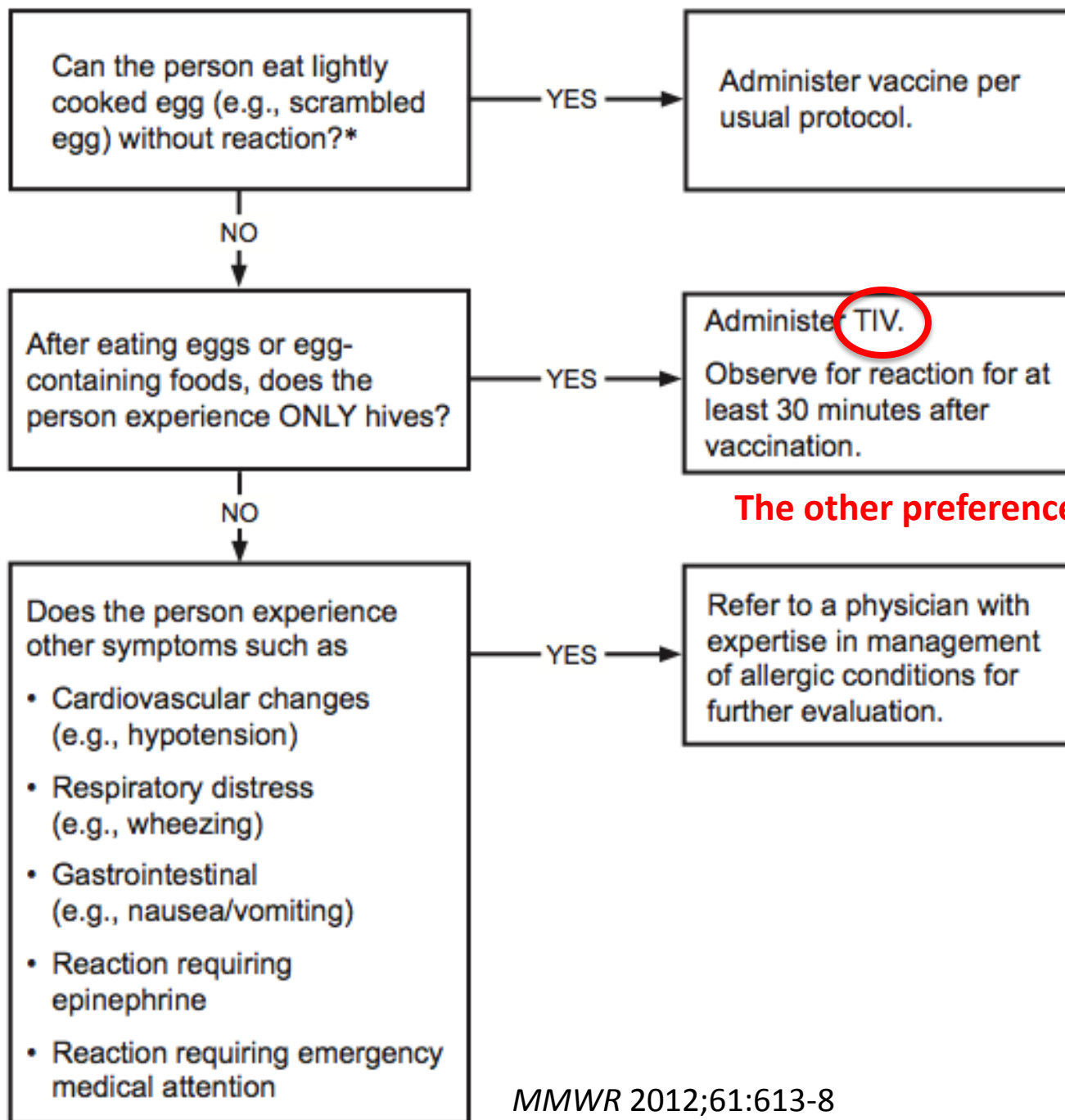
TABLE 1. Influenza Vaccines — United States, 2013–14 influenza season\*

Vaccine	Trade name	Manufacturer	Age Indication
Inactivated Influenza Vaccine, Trivalent <sup>†</sup> (IIV3), Standard Dose	Afluria <sup>®</sup>	CSL Limited	<u>&gt;</u> 9 yrs
	Fluarix <sup>®</sup>	GlaxoSmithKline	<u>≥</u> 3 yrs
	Flucelvax <sup>®§§§</sup>	Novartis Vaccines	<u>≥</u> 18 yrs
	FluLaval <sup>®</sup>	ID Biomedical Corporation of Quebec (distributed by GlaxoSmithKline)	<u>≥</u> 18 yrs
	Fluvirin <sup>®</sup>	Novartis Vaccines	<u>≥</u> 4 yrs
	 Fluzone <sup>®</sup>	Sanofi Pasteur	<u>≥</u> 6 months
	Fluzone <sup>®</sup> Intradermal <sup>§</sup>	Sanofi Pasteur	18 yrs through 64 yrs
Inactivated Influenza Vaccine, Trivalent <sup>†</sup> (IIV3), High Dose	Fluzone <sup>®</sup> High-Dose <sup>**</sup>	Sanofi Pasteur	<u>≥</u> 65 yrs
Inactivated Influenza Vaccine, Quadrivalent <sup>†</sup> (IIV4), Standard Dose	 Fluarix <sup>®</sup> Quadrivalent	GlaxoSmithKline	<u>≥</u> 3 yrs
	Fluzone <sup>®</sup> Quadrivalent	Sanofi Pasteur	<u>≥</u> 6 months
Recombinant Influenza Vaccine, Trivalent <sup>+++</sup> (RIV3)	FluBlok <sup>®</sup>	Protein Sciences	18 yrs through 49 yrs
Live-attenuated Influenza Vaccine, Quadrivalent <sup>+++</sup> (LAIV4)	 FluMist <sup>®</sup> Quadrivalent <sup>++</sup>	MedImmune	2 yrs through 49 yrs

# Who Should Be Vaccinated?

- 1960: first national recommendations published in *Public Health Reports*; based on epidemiology of 1957 pandemic:
  - Persons with chronic diseases
  - Persons aged  $\geq 65$  years
  - Pregnant women
- 1984: health care workers, anyone who wishes to reduce their risk
- 1986: household contacts and caregivers of high-risk persons
- 2000: persons aged  $\geq 50$  years
- Next 10 years: continually expanding recommendations
- 2010: practically everyone aged  $\geq 6$  months
- 2012: new recommendations for patients with history of egg allergy

## Who Should Be Vaccinated?



The other preference for IIV over LAIV



# Use of New Vaccines in Persons With Egg Allergy

- cclIV
  - Licensed for persons aged  $\geq 18$  years
  - Seed viruses passaged in eggs prior to propagation in canine kidney cells
  - Trace ovalbumin
  - Use in egg allergy not addressed in package insert
  - ACIP: “administer according to the guidance for other IIVs”
- RIV
  - Licensed for persons aged 18-49 years
  - “May be administered to people with egg allergy of any severity”

# Influenza Vaccine in Pregnancy

- Risk of medically attended influenza and fetal death among 117,347 pregnant women in Norway during 2009 pandemic
  - 54% vaccinated during 2<sup>nd</sup> or 3<sup>rd</sup> trimester
  - Vaccine effectiveness 70% (95% CI 66% to 75%)
  - Hazard ratio of fetal loss:
    - Vaccination: 0.88 (95% CI 0.66 to 1.17)
    - Influenza: 1.91 (95% CI 1.07 to 3.41)
- Among Bangladeshi infants born to women vaccinated with IIV in 3<sup>rd</sup> trimester, 63% less lab-confirmed influenza during first 6 months of life
- Benefits of vaccinating pregnant women
  - Less influenza illness and risk of death
  - Less fetal loss due to influenza
  - Protection during the 1<sup>st</sup> 6 months of life



Håberg SE, et al. *N Engl J Med* 2013;368:333-40

Zaman K, et al. *N Engl J Med* 2008; 359:1555-64

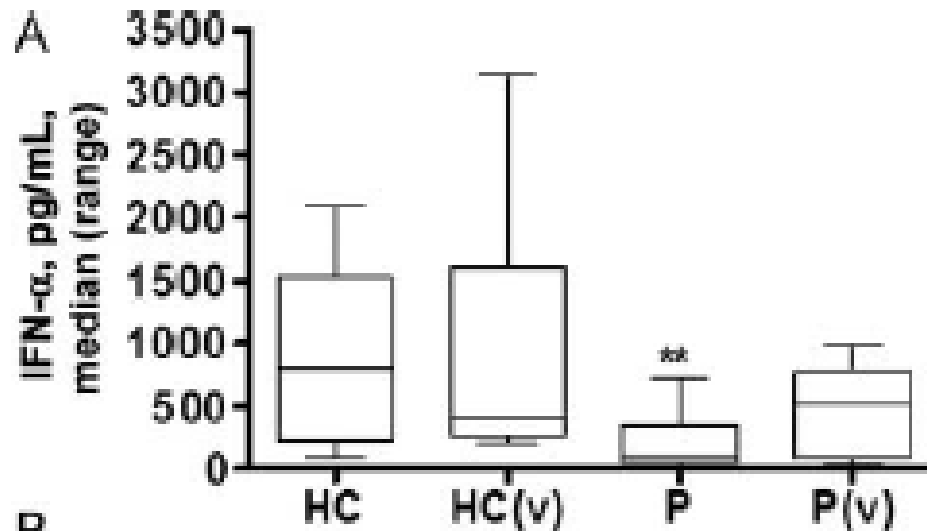
# Influenza Vaccine in Pregnancy

- IIV recommended by ACIP and ACOG for women who are or will be pregnant during influenza season
- May be administered any time in pregnancy, before or during influenza season
- LAIV not recommended for pregnant woman, but may be administered post-partum



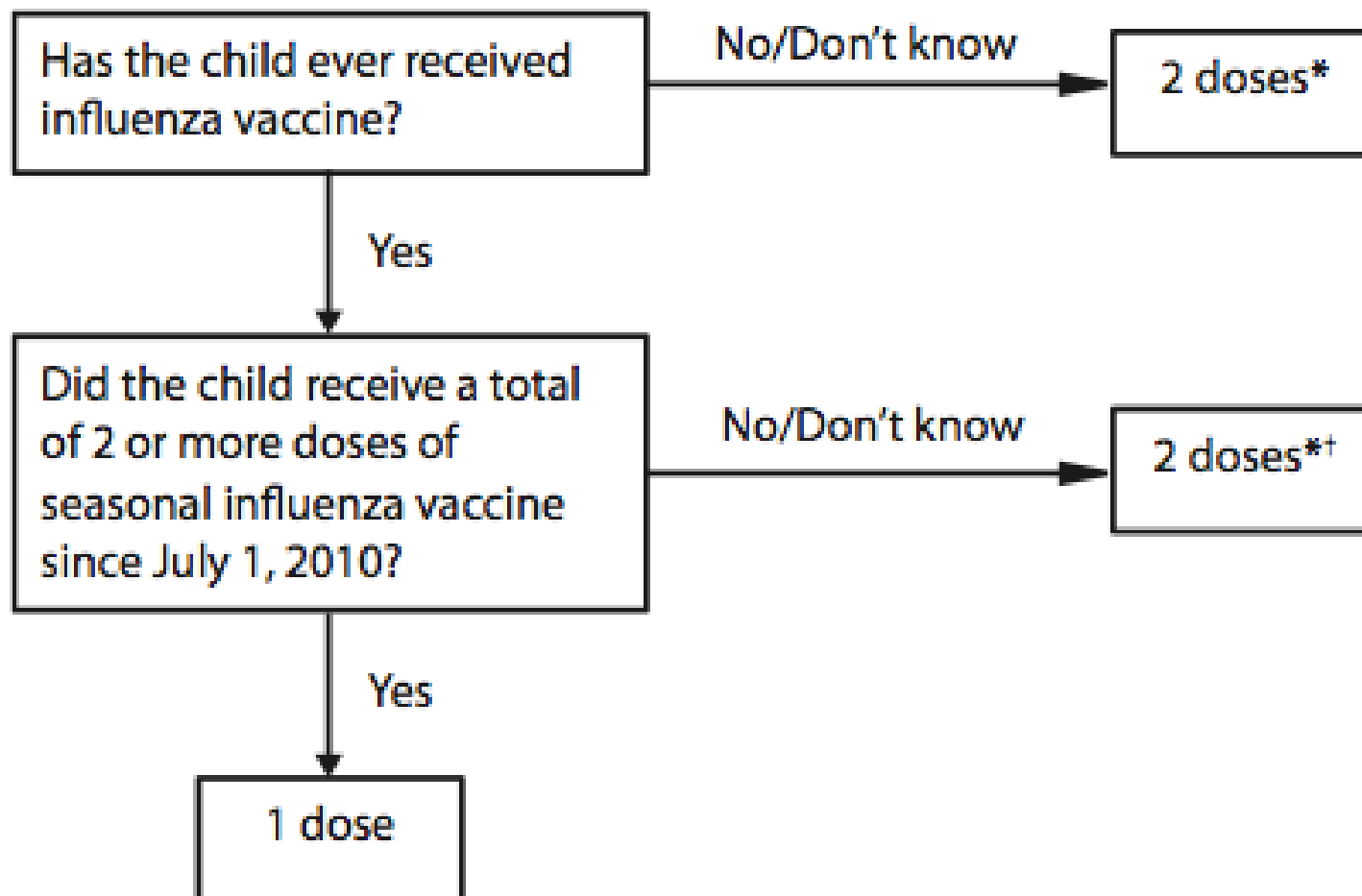
# Pregnancy and Influenza

- More than just reduced pulmonary capacity...



- PBMCs from pregnant women show attenuated interferon response following stimulation with H1N1 A/2009
- Response is improved following vaccination

# Vaccinating Children Age 6 Months Through 8 Years



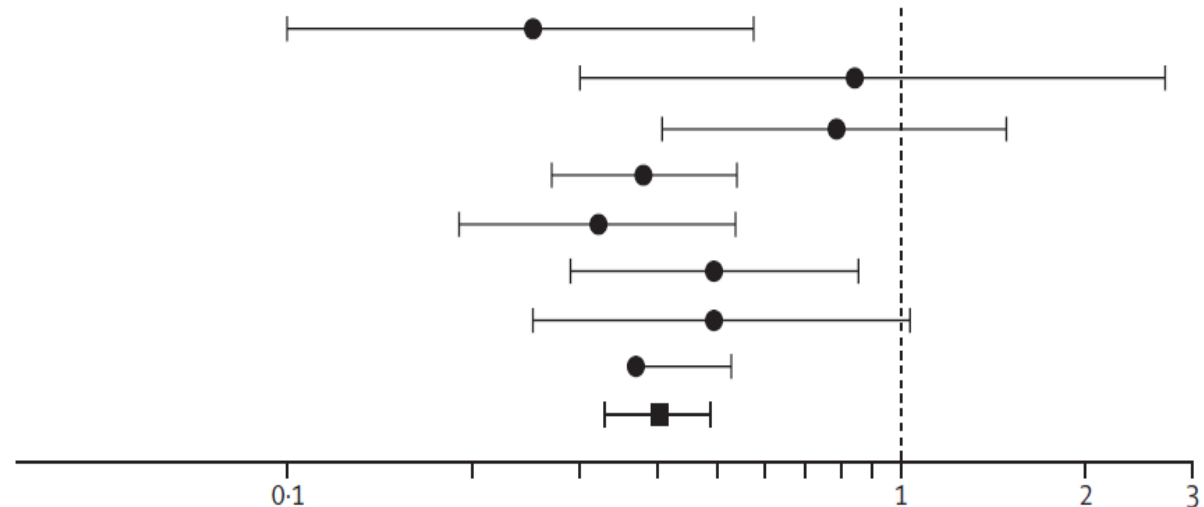
# Challenges in Evaluating Influenza Vaccines

- Effectiveness is variable year-to-year
- Antibody response to HA may not reflect full spectrum of protection
  - NA
  - Cellular immunity
- End points:
  - ILI: self-reported, medically attended, etc.
  - Confirmed influenza infection
  - School or work attendance
  - Mortality: P&I, all-cause

# Meta-Analysis of RCTs of Influenza Vaccines Published Between Jan 1967 and Feb 2011

- Trials in 8 influenza seasons of IIV3 in adults aged 18-64 years:

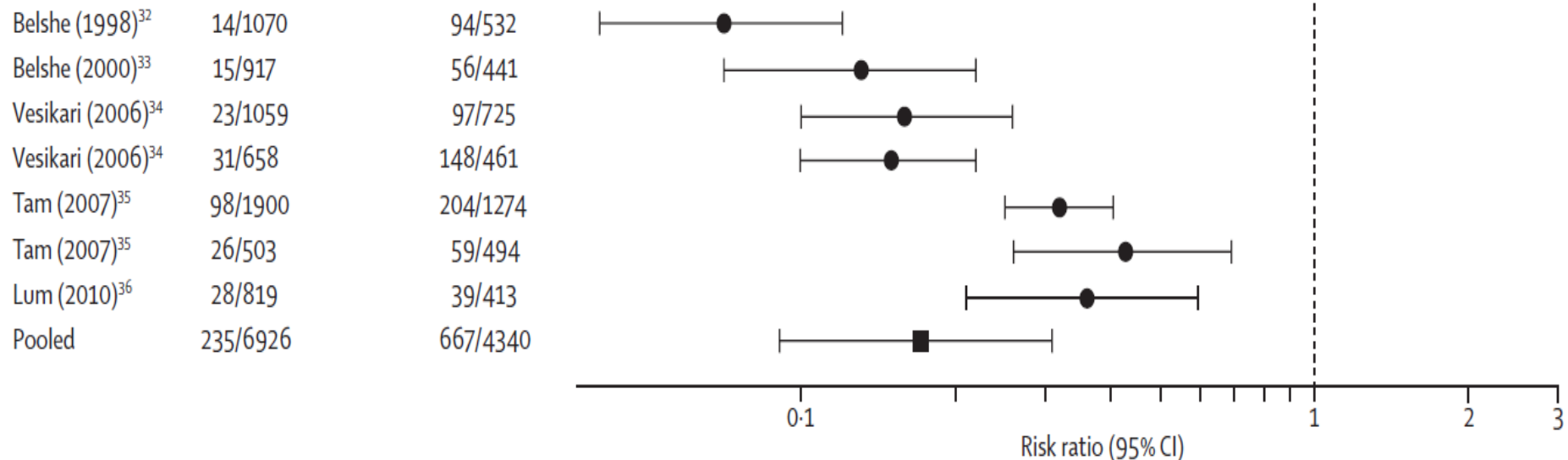
Ohmit (2006) <sup>24</sup>	10/522	16/206
Ohmit (2008) <sup>25</sup>	13/867	6/338
Beran (2009) <sup>26</sup>	28/4137	18/2066
Beran (2009) <sup>27</sup>	63/5103	82/2549
Monto (2009) <sup>28</sup>	28/813	35/325
Jackson (2010) <sup>21</sup>	19/1706	38/1725
Jackson (2010) <sup>21</sup>	11/2011	22/2043
Frey (2010) <sup>29</sup>	49/3638	140/3843
Pooled	221/18797	357/13095



- Pooled vaccine efficacy 59% (95% CI 51%-67%)

# Meta-Analysis of RCTs of Influenza Vaccines Published Between Jan 1967 and Feb 2011

- Trials in 7 influenza seasons of LAIV3 in children aged 6 months to 7 years:



- Pooled vaccine efficacy 83% (95% CI 69%-91%)**

# Influenza Vaccine Effectiveness Network, 2012-13, 2,697 Patients with ARI

	Influenza + % Vaccinated	Influenza – % Vaccinated	Vaccine Effectiveness (95% CI)
Overall	33%	50%	56% (47%-63%)
6 mon-17 yrs	26%	49%	64% (51%-73%)
18 yrs-49 yrs	28%	42%	52% (38%-79%)
50 yrs-64 yrs	36%	58%	63% (43%-76%)
≥65 yrs	69%	72%	27% (-31%-59%)
Influenza A-H3N2	39%	50%	47% (35%-58%)
Influenza B	25%	47%	67% (51%-78%)

# Influenza Vaccine Safety

- Over 1 Billion doses administered since 1990
- GSB:
  - 1976: 9-fold increased risk over baseline of <1/million
  - 2009: 1 excess case of GBS/1 million vaccinated
- Ontario 1993-2011, GBS attributable risk following vaccination and influenza infection:
  - 1.03 cases/1,000,000 vaccinees; risk greatest 2-4 weeks after vaccination
  - 17.2 cases/1,000,000 influenza cases
- ACIP: history of GBS within 6 weeks of a previous dose is contraindication to any influenza vaccine

# Vaccine Safety Pop-Quiz

- Q: recipients of what vaccine will experience:
  - 2 cases of Guillain-Barré Syndrome within 6 weeks per 1,000,000 persons vaccinated
  - 43 spontaneous abortions within 24 hours per 100,000 pregnant women vaccinated

# Vaccine Safety Pop-Quiz

- Q: recipients of what vaccine will experience:
  - 2 cases of Guillain-Barré Syndrome within 6 weeks per 1,000,000 persons vaccinated
  - 40 spontaneous abortions within 24 hours per 100,000 pregnant women vaccinated
- A: Placebo

# The New York Times

Are The Vaccines Safe?

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MONDAY, SEPTEMBER 28, 2009

## Swine Flu Officials' Message: Don't Blame Shots for All Ills

By DONALD G. McNEIL Jr.

As soon as swine flu vaccinations start next month, some people getting them will drop dead of heart attacks or strokes, some children will have seizures and some pregnant women will miscarry.

But those events will not necessarily have anything to do with the vaccine. That poses a public relations challenge for federal officials, who remember how sensational reports of deaths and illnesses derailed the large-scale flu vaccine drive of 1976.

This time they are making plans to respond rapidly to such events and to try to reassure a nervous public — and headline-hunting journalists — that the vaccine is not responsible.

Every year, there are 1.1 mil-

lion heart attacks in the United States, 795,000 strokes and 876,000 miscarriages, and 200,000 Americans have their first seizure. Inevitably, officials say, some of these will happen within hours or days of a flu shot.

The government "is right to expect coincident deaths, since people are dying every day, with or without flu shots," said Dr. Harvey V. Fineberg, president of the Institute of Medicine and co-author of "The Epidemic That Never Was," a history of the 1976 swine flu vaccination campaign.

Officials are particularly worried about spontaneous miscarriages, because they are urging pregnant women to be among the first to be vaccinated. Pregnant

*Continued on Page A14*

### QUOTATION OF THE DAY

*“There are about 2,400 miscarriages a day in the U.S. You’ll see things that would have happened anyway. But the vaccine doesn’t cause miscarriages. It also doesn’t cause auto accidents, but they happen.”*

*DR. JAY C. BUTLER,  
of the federal Centers for  
Disease Control and Preven-  
tion, on people’s fears about  
being vaccinated. [A14]*

# Can Influenza Vaccine Give You The Flu?: Some Mechanistic Considerations

Mechanism of Action	Comment
The vaccine itself causes the influenza infection	Inactivated viral subunits or attenuated viruses
The vaccine causes non-infectious ILI	Oculo-respiratory syndrome*
The vaccine increases susceptibility to infection with circulating influenza viruses	Not supported by studies of efficacy or effectiveness
The vaccine increases susceptibility to infection with other respiratory pathogens	Two possible explanations: 1.Vaccine decreases non-specific immunity, or 2. Influenza infection activates non-specific immunity; thus, vaccination, by preventing influenza infection paradoxically increases risk of infection with other viruses

\*Red eyes, cough, sore throat 2-24 hours after receipt of 2000-01 Shire Biologics' Fluviral® in Canada (NACI *Can Commun Dis Rep* 2001;27:1–3)

# Influenza Vaccination and Risk of Non-Influenza Respiratory Viruses

- Patients presenting to Marshfield Clinic with ARI, 2004-05 through 2009-10 seasons
- 2010 ARIs in children aged <5 years
- 1738 ARIs in adults aged ≥50 years
- Tested by RT-PCR:

Influenza A and B

RSV A and B

Rhinovirus

Human Metapneumovirus

Parainfluenza 1-4

Adenovirus B and E

CoV O43, NL63, HKU1, 229E

# Influenza Vaccination and Risk of Non-Influenza Respiratory Viruses

- Influenza detected:
  - 251 (12.5%) children
  - 343 (19.7%) adults
- Non-influenza viruses detected:
  - 1411 (70.2%) children
  - 659 (37.9%) adults
  - RSV, rhinovirus, hMPV most common
- No association between influenza vaccination and infection with single non-influenza virus, *except*
- Parainfluenza infection in 4.6% of vaccinated and 6.7% unvaccinated children ( $p=0.03$ )
- Parainfluenza infection in 4.6% of vaccinated and 2.6% of unvaccinated adults ( $p=0.04$ )

# Influenza Vaccination and Risk of Non-Influenza Respiratory Viruses

- In case you were wondering...

Age Group	Adjusted Vaccine Efficacy	95% Confidence Interval
Children	48%	31% - 61%
Adults	44%	25% - 58%

*Aren't There Better Alternatives to Vaccines?*



*Aren't There Better Alternatives to Vaccines?*



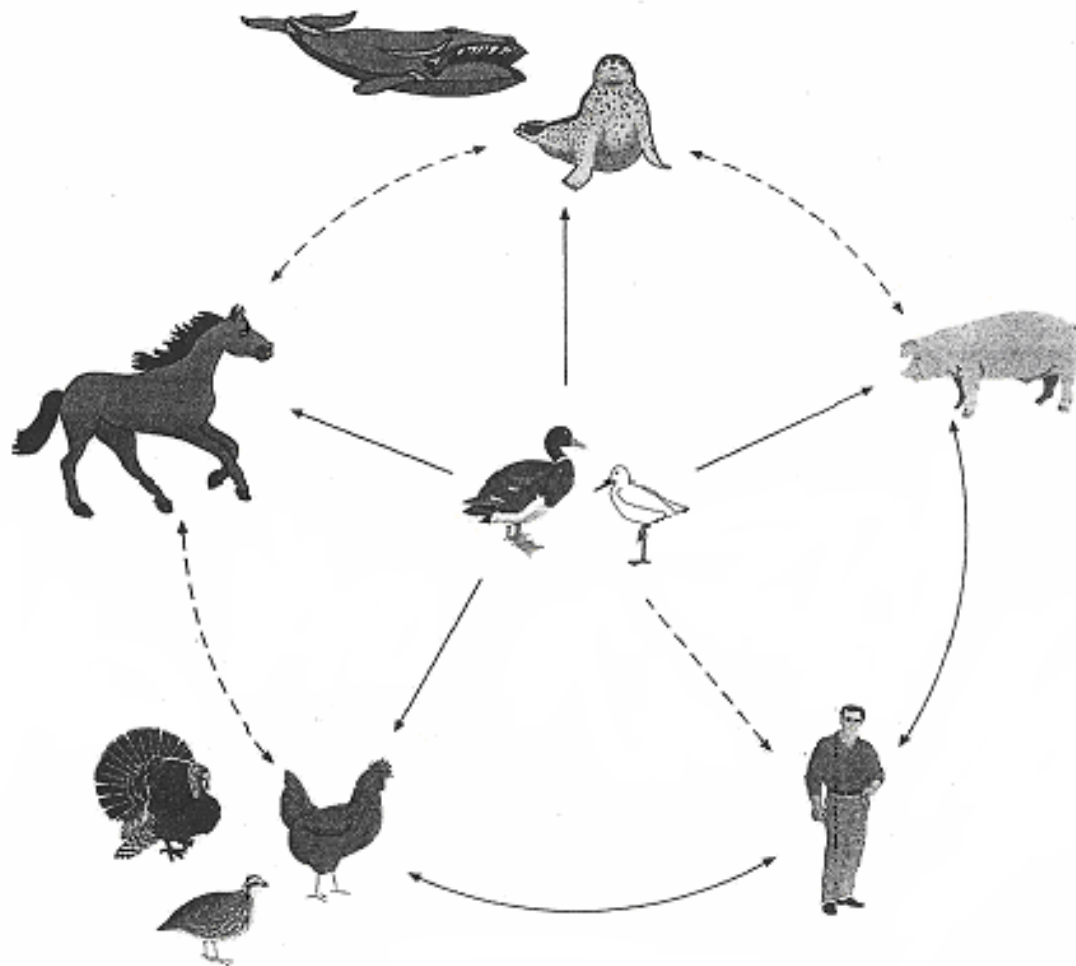
# New and Better Vaccines?

- New delivery methods
- Antigen sparing adjuvants:
  - Used in 2009 pandemic in Europe
  - Possible link between AS03 to narcolepsy in Finland
- Universal vaccines:
  - Directed at highly conserved epitope, e.g. matrix protein (M2)
  - Stimulate cellular immunity
    - Study of 342 healthy UK adults during 2009 pandemic
    - Incident pH1N1 infection milder among those with greater frequencies of pre-existing select CD-8 T cells



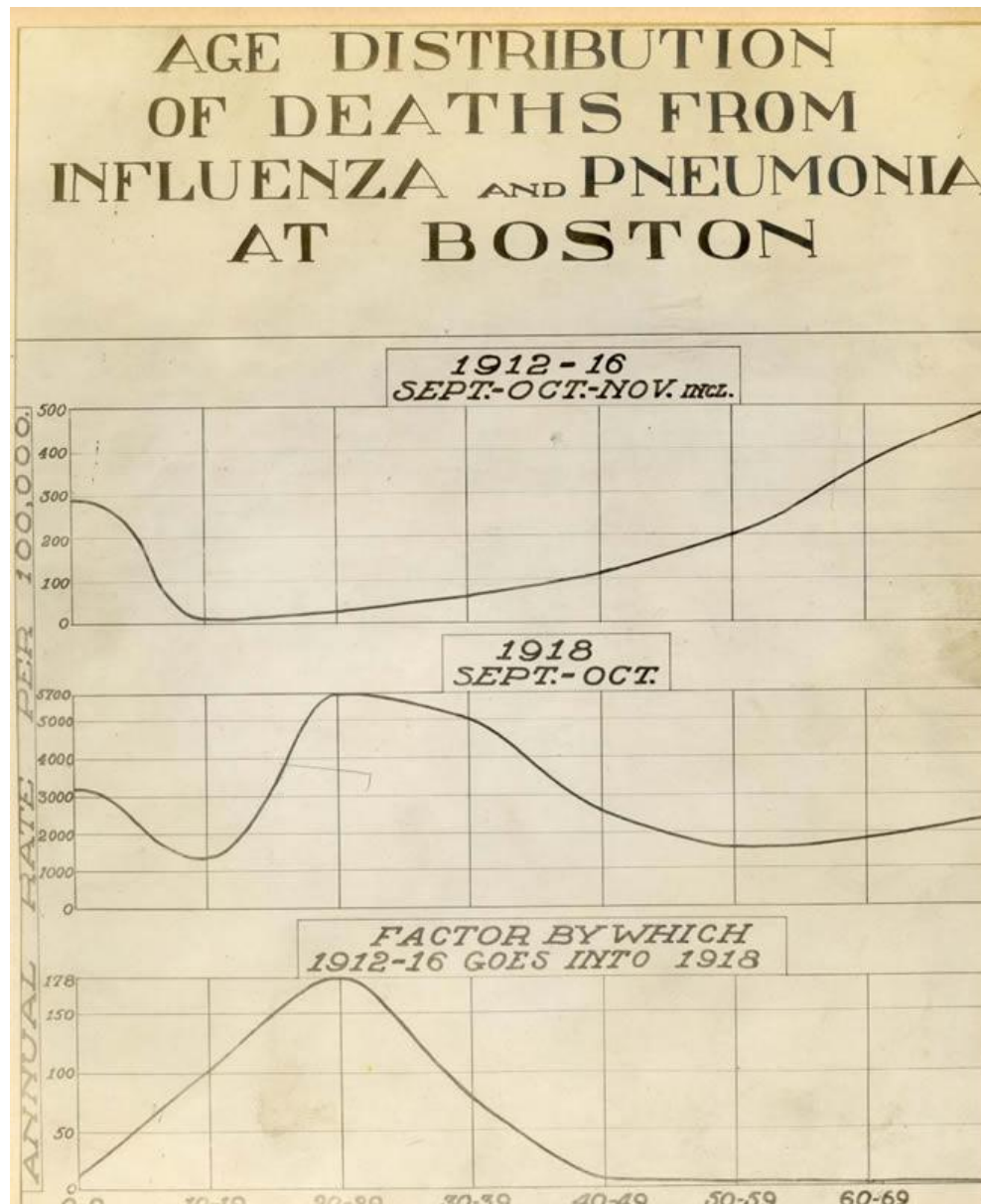
Soluvia®  
microinjection  
system for ID  
administration,  
BD

# New and Worse Viruses?



“Predictably unpredictable”

# New and Worse Viruses?



Graph  
courtesy of  
Dr. Mike  
Osterholm

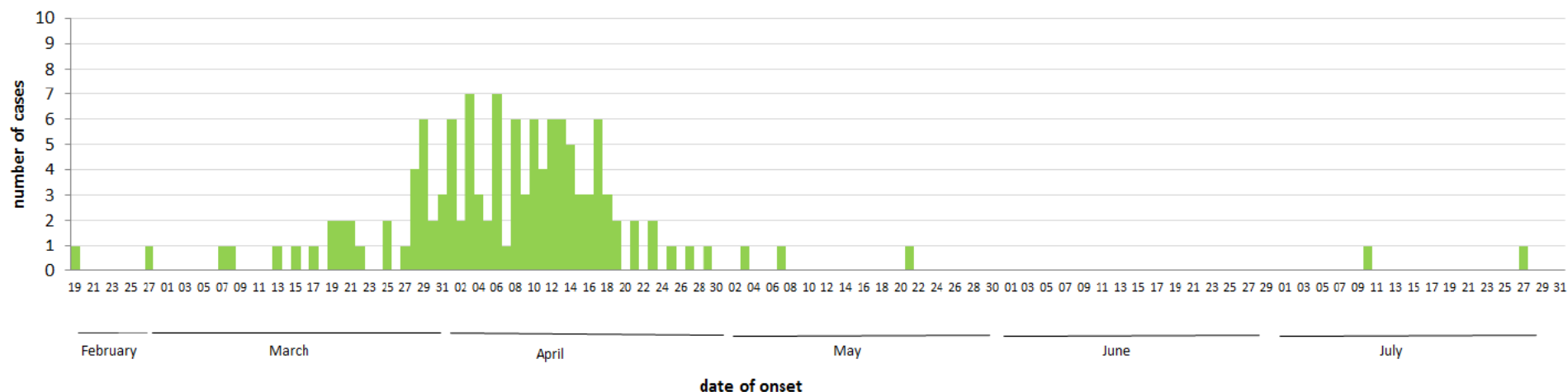
# New and Worse Viruses?

Confirmed human cases of avian influenza A(H7N9) reported to WHO



# Epidemiological curve of confirmed cases of avian influenza A(H7N9) reported to WHO, by day, 2013

**N = 125 confirmed cases for whom date of onset is known**

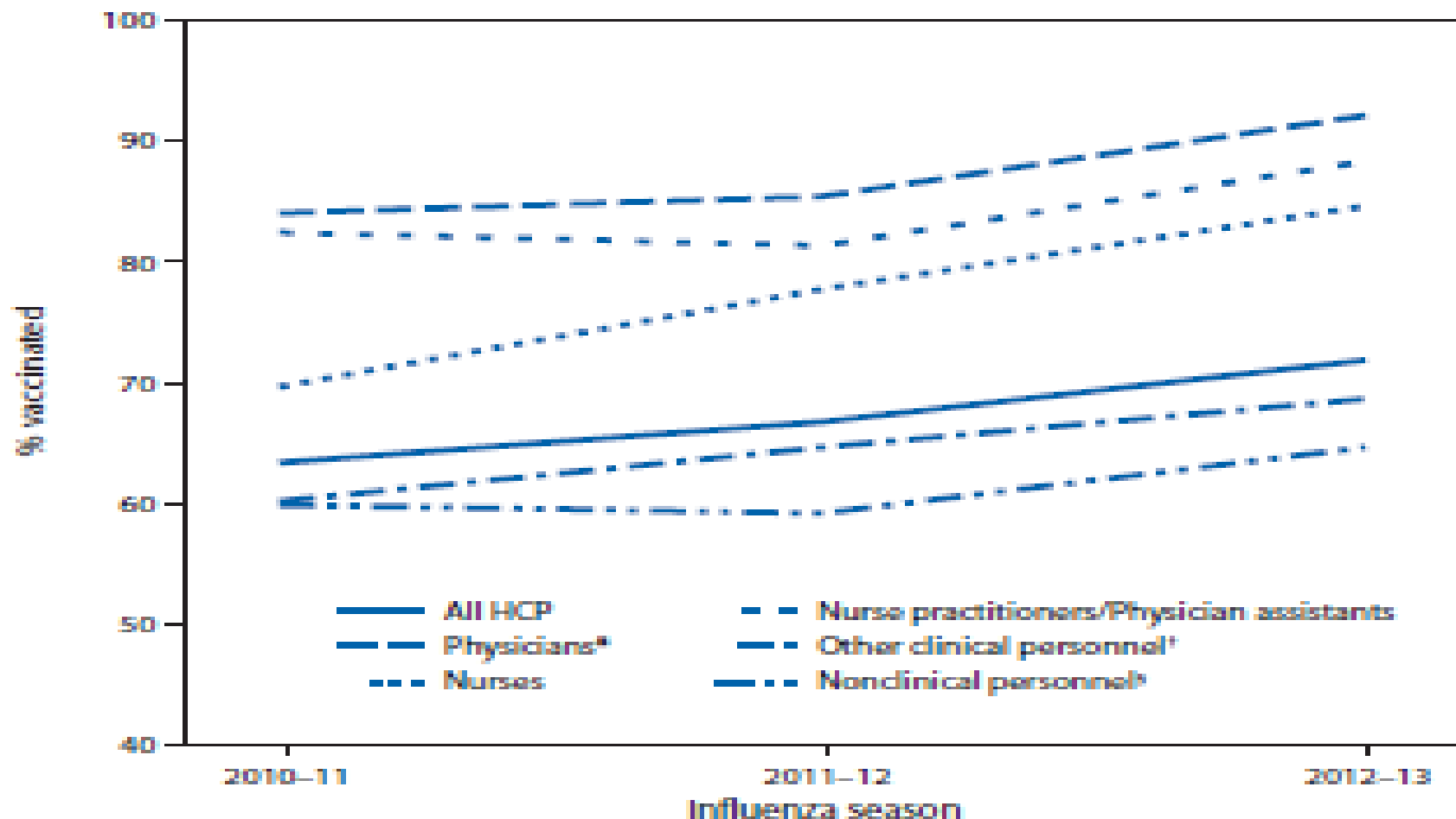


All dates refer to onset of illness

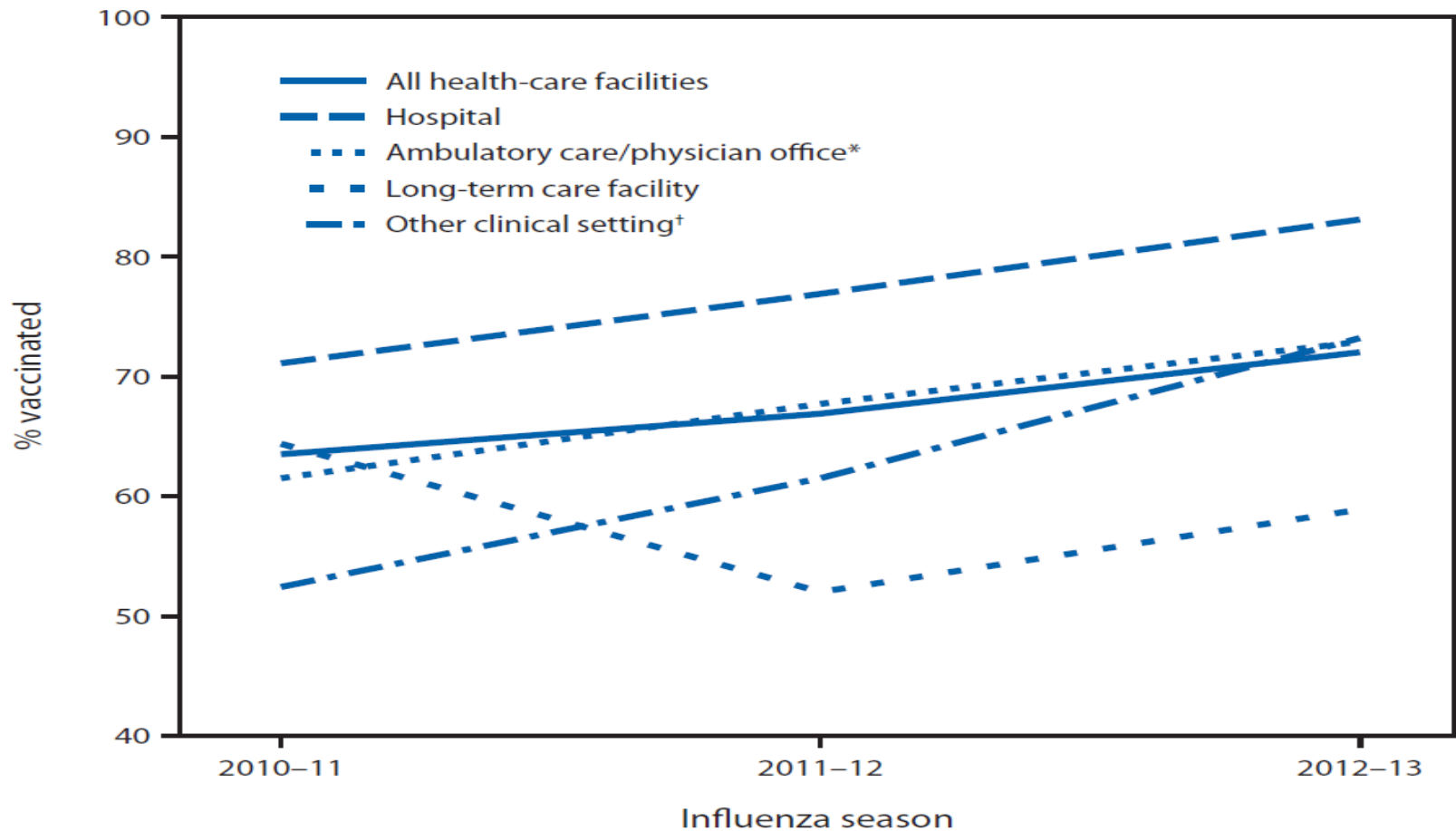
Data in WHO/HQ as of 12 August 2013, 14:45 GMT+1

Source: WHO/GIP

# Vaccine Coverage Among Healthcare Providers, US, 3 Seasons, 2010-13



# Vaccine Coverage Among Healthcare Facilities, US, 3 Seasons, 2010-13



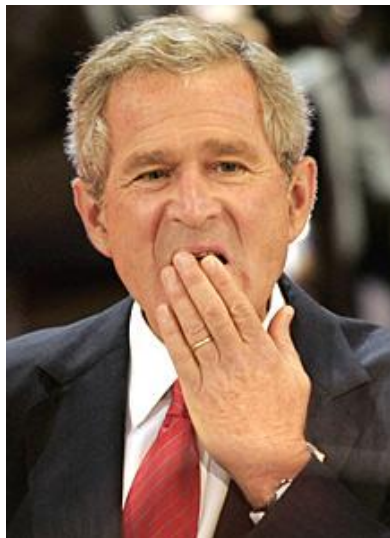
# What Is The Greatest Threat?



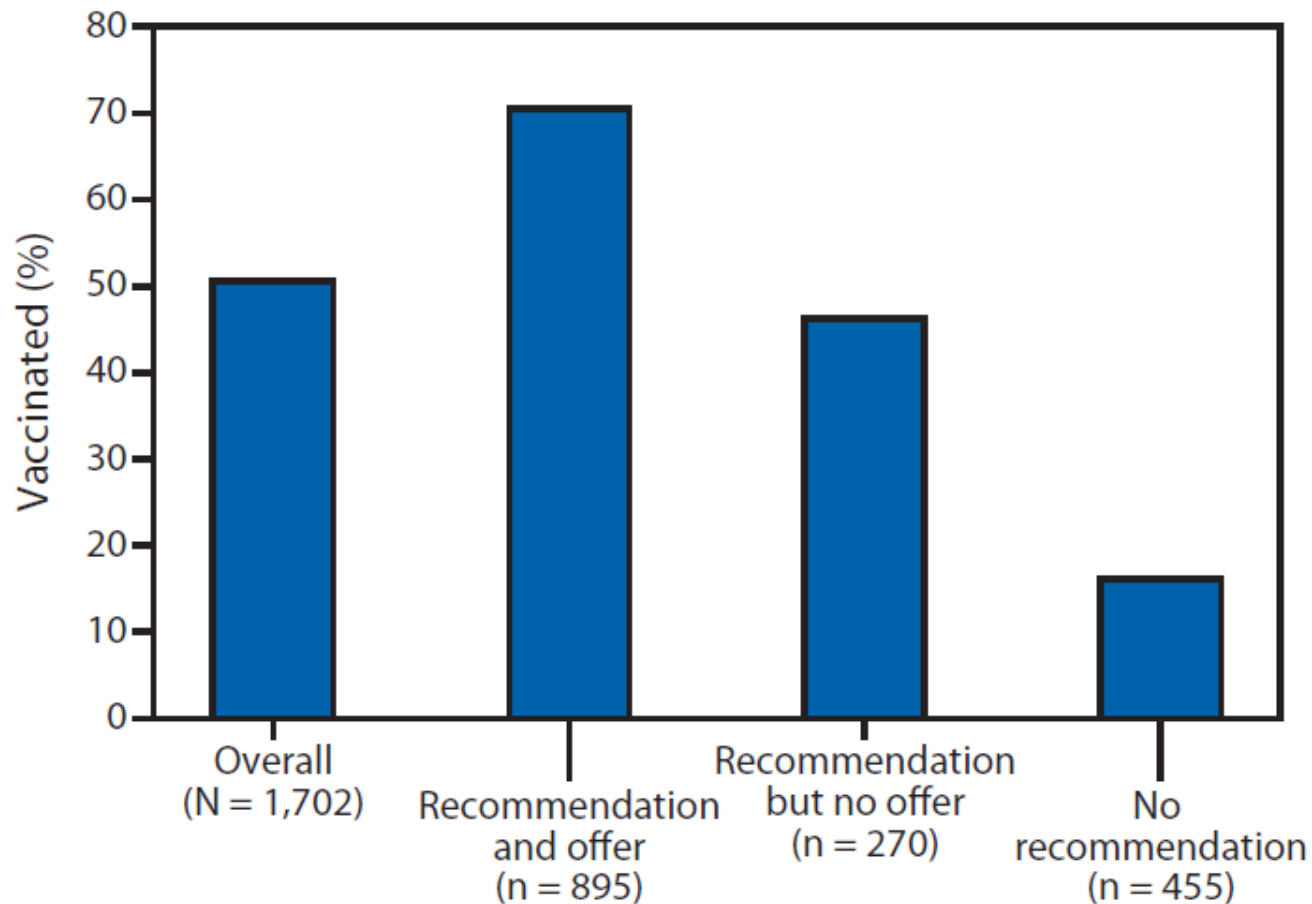
Handel Ngary/Getty Images

# Greatest Challenge to Immunization Programs

- Apathy

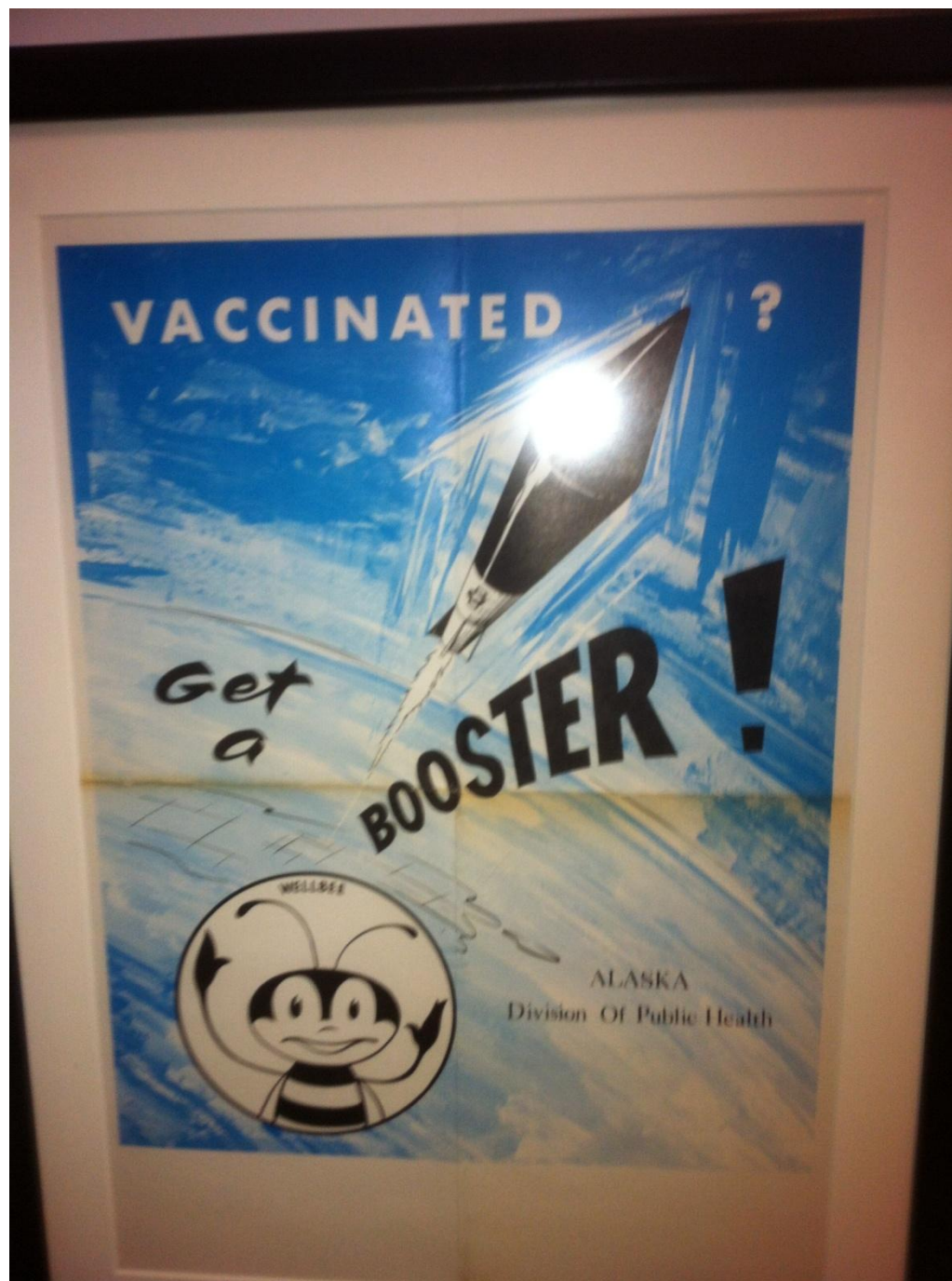


# Influenza Immunization Among 1,702 Pregnant Women, US, 2012-13: Effect Of Provider Recommending and Offering Vaccine



# The Most Ineffective and Dangerous Vaccines in the World





Alaska Division  
of Public Health  
Poster, circa  
1962 at the  
Global Health  
Odyssey, CDC,  
Atlanta